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QUANTUM MECHANICS SIMULATION OF CADMIUM(II) TRIPEPTIDE COMPLEXES

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By

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Chairman : Professor Mohd Basyaruddin Bin Abdul Rahman, PhD
Faculty : Science

Cadmium detection in aqueous medium is an important step in attempt to avoid human exposure to the extremely toxic metal. It is believed that one of the significant qualitative detection processes of cadmium(II) can be performed using a biosensor with the help of small peptides as the biological material. The current issue is that proper peptides to capture cadmium(II) are still unknown, since there is not enough information about the interaction between the metal ion and most of the small peptides in literature. Quantum mechanics methods, such as Density Functional Theory (DFT), can be employed to understand the electronic interaction between cadmium(II) and the peptides. Minnesota 06 functional (M06) in combination with Default 2 triple zeta plus polarization (Def2TZVP) basis set was denoted as the best method among those, which were employed in this research to describe properties of several cadmium complexes, such as Cd-S bond length and S-Cd-S bond angle. For this purpose, data on cadmium(II) benzenthiolato was extracted from Cambridge Structural Database (CSD) and compared to the computed data on the same molecule achieved theoretically using Becke Three Parameter Hybrid Functional in combination with Double zeta split-valence plus polarization basis set (B3LYP/DGDZVP) and M06/Def2TZVP. The results from the second method yielded 2.66% of errors for Cd-S bond lengths and 2.87% of errors for S-Cd-S bond angles, while in the presence of DGDZVP basis set in combination with B3LYP the errors rose up to 5.17% in Cd-S bond lengths and 4.90% in S-Cd-S bond angles. Cadmium(II) complexes with the small peptides, such as dipeptide, tripeptide and tetrapeptide were optimized employing M06/Def2TZVP and Polarizable Continuum Method (PCM) to determine the peptide length effect on the Cd-S binding energy. Cd-S binding energy in the tripeptide, if compared with the dipeptide and the tetrapeptide, was bigger as much as 12.62 kJ and 5.82 kJ respectively. Therefore, Cd-S binding energy of different tripeptide sequences were screened by fixing cysteine in the terminals and changing the middle amino acid to each one of the twenty essential amino acids. The optimization was performed in

vacuum using B3LYP/DGDZVP and M06/Def2TZVP methods. The procedures were repeated using PCM, in which water was chosen as the solvent, to investigate dielectric effect of water molecules on the Cd-S moiety. Cd-S binding energy of Cysteine-Proline-Cysteine (CPC) is the highest, if compared to the other observed nineteen tripeptides with the binding energies of 285.98 kJ in the presence of PCM using M06/Def2TZVP. The computed bond lengths between the metal ion and the sulfur atoms, using M06/Def2TZVP, are between 2.353 Å to 2.476 Å in vacuum, and 2.434 Å to 2.451 Å with PCM. Thus, CPC peptide could serve as biological material in the cadmium(II) biosensor application.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Master Sains

SIMULASI MEKANIK KUANTUM KOMPLEKS KADMIUM (II) TRIPEPTIDA

Oleh

SHAHO MOHAMMED ABDALLA

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Pengerusi : Profesor Mohd Basyaruddin Bin Abdul Rahman, PhD
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Pengesanan logam kadmium dalam medium akueus adalah satu langkah penting dalam usaha untuk mengelakkan pendedahan logam yang sangat toksik kepada manusia. Penderia bio merupakan salah satu teknik pengesanan kualitatif bagi kadmium(II) boleh dilakukan dengan menggunakan peptida pendek sebagai bahan biologi. Walaubagaimanpun maklumat berkaitan peptida yang sesuai untuk mengesan kadmium(II) masih tidak diketahui, kerana tidak ada maklumat yang cukup tentang interaksi antara ion logam dan peptida kecil dalam rujukan ilmiah. Kaedah Kuantum Mekanik (QM), seperti Teori Fungsi Ketumpatan (DFT) boleh digunakan untuk memahami interaksi elektronik di antara kadmium(II) dan peptida. Pemfungsian Minnesota 06 (M06) dengan kombinasi set asas Lalai 2 Ganda Tiga Zeta Tambah Polarisasi (Def2TZVP) didapati merupakan kaedah terbaik dalam kajian ini untuk menggambarkan sifat-sifat kompleks kadmium, seperti panjang ikatan Cd-S dan sudut ikatan S-Cd-S. Untuk tujuan ini, data mengenai kadmium(II) benzentiolato daripada Pangkalan Data Struktur Cambridge (CSD) telah digunakan dan dibandingkan dengan perkiraan data pada molekul yang sama secara teori menggunakan Pemfungsian Hibrid Tiga Parameter Becke dengan kombinasi set asas Ganda Dua Zeta Belah-Valens Tambah Polarisasi (B3LYP/DGDZVP) dan M06/Def2TZVP. Keputusan daripada kaedah kedua memberikan ralat sebanyak 2.66% bagi panjang ikatan Cd-S dan 2.87% bagi sudut ikatan S-Cd-S, manakala dengan menggunakan set asas DGDZVP dengan kombinasi B3LYP pula ralat didapati telah meningkat sehingga 5.17% bagi panjang ikatan Cd-S dan 4.90% bagi sudut ikatan S-Cd-S. Kompleks Kadmium(II) dengan peptida kecil, seperti dipeptida, tripeptida dan tetrapeptida telah dioptimumkan menggunakan M06/Def2TZVP dan Kaedah Pengkutuban Berterusan (PCM) untuk menentukan kesan panjang ikatan peptida terhadap tenaga ikatan Cd-S. Tenaga pengikatan logam bagi tripeptida, jika dibandingkan dengan dipeptida dan tetrapeptida didapati lebih besar sehingga 12.62 kJ dan 5.82 kJ, masing-masing. Oleh itu, tenaga pengikatan logam Cd-S bagi tripeptida yang berbeza telah disaring dengan menetapkan sistina

pada kedua-dua terminal dan menukar asid amino tengah bagi tengah dengan 19 asid amino penting. Prosedur tersebut diulang menggunakan PCM, di mana air telah dipilih sebagai pelarut, untuk mengkaji kesan dieletrik molekul air pada moieti Cd-S. Tenaga pengikatan Cd-S bagi Sistina-Prolina-Sistina (CPC) adalah yang tertinggi jika dibandingkan dengan 19 tripeptida lain dengan tenaga ikatan 285.98 kJ dalam PCM dengan menggunakan M06/Def2TZVP. Pengiraan panjang ikatan di antara ion logam dan atom-atom sulfur menggunakan M06/Def2TZVP memberikan nilai di antara 2.353 Å hingga 2.476 Å dalam vakum, dan 2.434 Å hingga 2.451 Å dalam PCM. Justeru, peptida CPC boleh dijadikan sebagai bahan biologi dalam aplikasi penderia bio kadmium(II).

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

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LIST OF ABBREVIATIONS

ATSDR	Agency for Toxic Substances and Disease Registry
IARC	International Agency for Research on Cancer
ICP-MS	Inductively coupled plasma mass spectrometry
GFAAS	Graphite furnace atomic absorption spectroscopy
ESIMS	Electrospray Ionization Mass Spectrometry
NMR	Nuclear Magnetic Resonance
ROS	Reactive oxygen species
CD	Circular dichroism
MT	Metallothionein
DFT	Density functional theory
HF	Hartree-Fock
CPCM	Conductor-like Polarizable Continuum Model
PCM	Polarizable continuum model
CSD	Cambridge structural data base
IUPAC	International Union of Pure and Applied Chemistry
ISFET	Ion-sensitive field-effect transistor
ISE	Ion selective electrode
ENFET	Enzyme field-effect transistor
IMFET	Immunological field-effect transistor
B3LYP	Becke Three Parameter Hybrid Functional
M06	Minnesota 06 functional
Def2TZVP	Default 2 triple zeta plus polarization basis set
Def2SVP	Default 2 Split Valence plus Polarization
DGDZVP	Double zeta split-valence plus polarization basis set

Cys	Cysteine
His	Histidine
Ile	Isoleucine
Met	Methionine
Ser	Serine
Val	Valine
Ala	Alanine
Gly	Glycine
Leu	Leucine
Pro	Proline
Thr	Threonine
Arg	Arginine
Asn	Asparagine
Asp	Aspartate
Glu	Glutamate
Gln	Glutamine
Phe	Phenylalanine
Tyr	Tyrosine
Trp	Tryptophan
Lys	Lysine

CHAPTER 1

INTRODUCTION

Cadmium lies at the end of the second row of transition metals in the periodic table. Since it has filled 'd' shell orbitals, it has a variety of coordination systems such as three coordination numbers (Matzapetakis et al., 2002), four coordination numbers (Shindo & Brown, 1965), and six coordination numbers (Barrie et al., 1993). Cadmium(II) is the most abundant oxidation state of cadmium ions in nature, although cadmium(I) oxidation state is recorded by dissolving cadmium in a mixture of cadmium chloride and aluminum chloride (Holleman *et al*., 1985). Cadmium is widely used by people due to its applicability, for instance, in industry as Ni-Cd batteries and coloring agents, and in agriculture as phosphate fertilizers (McLaughlin & Singh, 1999). In addition, semiconductor cadmium chalcogenide nanocrystals (CdS, CdSe, and CdTe) have recently emerged as attractive materials for biological probes, since they have unique photo-physical characteristics (Derfus *et al.*, 2004). Consequently, the number of sources of cadmium(II) exposure continues to increase around human, and the high level of cadmium(II) contamination in soil and crops has become a cause for concern, since it severely affects human health in case of overdose exposure.

Cadmium is ranked the seventh in the list of hazardous substances and environmental pollutants among 785 different chemicals (The ATSDR 2015 Substance Priority List, 2015). It is also classified by International Agency for Research on Cancer (IARC) as a human carcinogen causing tumors of lungs, prostate, injection site, and other tissues (Waalkes, 2003). Chronically it affects kidneys and damages their function (Lars Järup *et al*., 1998). Human absorbs cadmium either by ingestion or inhalation. However, an average non-smoker German citizen has a daily intake of 30 – 35 µg cadmium; 95% of this intake comes from food and drinks, but this range increases in the case of smoking (Godt *et al*., 2006). It enables us to draw a conclusion, that cadmium(II) detection in aqueous medium is a crucial step to avoid its toxicity toward human since human gets the toxic metal ion significantly from drinks. As it is suggested by scholars, one of the significant detection processes of cadmium(II) could be done by using biosensor with the help of peptides as the biological material. Cadmium(II) can be detected by several other methods as well, for instance, Graphite furnace-atomic absorption spectrometry (GFAAS) (Ashraf, 2012) and inductively coupled plasma mass spectrometry (ICP-MS) (A. Sigel *et al.*, 2013). However, biosensor detection technique is cheaper and faster in comparison with the previous methods, if a qualitative detection process is required.

Biosensor is composed mainly of three parts: a receptor, a transducer and a digital monitor. The one, which is dwelled upon in this research is the receptor. The receptor can be enzymes or nucleic acids or antibodies (Chambers *et al*., 2002), or short peptides, used as the chelating agent to capture the substrates (Pavan & Berti, 2012).

However, proper biological materials to capture cadmium(II) are still under investigation. Steps in pursuit of such a chemical can give a significant result in serving the biosensor technology for detection of cadmium(II). In order to find a proper chemical for this purpose, a survey by the natural biological systems containing cadmium(II) can direct scientists toward prediction of a general structure to capture cadmium(II). Subsequently, computational chemistry methods can be employed to derive and predict the potential length and sequence of the detected structure from the natural systems theoretically.

Most of cadmium(II) in the living organs is bound to a small cysteine-rich, metal-binding protein called Metallothionein (MT) (Nordberg, 2004). MT was discovered in 1957 as a cadmium binding protein in horse kidney (Margoshes et al., 1957). MT is known as a crucial molecule to protect human health from toxicity of cadmium due to its tendency to capture it (Klaassen *et al.* , 2009). MT is one of the existing proteins in human body. Cysteine amino acids frequently repeat in MT sequence. Since naturally it can capture cadmium via its sulfur atom in cysteine amino acids, a part of its sequence (including L-cysteine) as a small peptide can be observed theoretically as the base for deriving the most eligible biological materials to be used in the production of cadmium(II) biosensor technology.

1.1. Problem Statements

Exact structural determination studies have not been published for the cadmium(II) complexes of the most common small peptide molecules (Sigel *et al*., 2013). Therefore, the lack of information about the binding energy of cadmium(II) with small peptides and the cadmium(II) peptide complexes with the lowest energy conformation in literature demands further investigation to explain the probability of using small peptides in cadmium(II) biosensor technology. Cadmium(II) tendency to bind with cysteine amino acids in the peptides and proteins was proved experimentally (Sutherland *et al*., 2011). Cysteine interacts with the metal ions via its sulfur atom, and the presence of cysteine in different peptides undoubtedly affects the metal binding energy with its sulfur atom. Thus, the process of binding of the metal with cysteine in different peptides needs further investigation and research.

1.2. Research Objectives

The objectives of this research are as follows:

- To investigate the effect of the peptide length on Cd-S binding energy.
- To investigate the tripeptides sequence effect on Cd-S binding energy.
- To select a proper theoretical method for calculating bond length and bond angle of cadmium(II) complexes among those, which were used.

Having adequate information about this interaction in hand, the most feasible peptide can be proposed for further observation to be constructed to interact with cadmium(II) as the biological chelating agent in the biosensors for detection of cadmium(II). The information can also aid to identify some properties of proteins, which contain this metal ion. For these purposes, one needs to understand the stability of the cadmium(II) peptide complexes and to describe it based on the energy of the complex system. The questions, such as, how the cadmium(II)-peptide interaction region affects the whole complex system, how much the bond energy is and what the range of the bond length is, should be answered adequately and thoroughly.

To sum up, this research covers a theoretical study about the interaction between cadmium(II) and deprotonated cysteine using density functional theory (DFT) (Hohenberg & Kohn, 1964). Changes in the energy of the system can give us the idea of which reaction process is the most appropriate one by cadmium(II) in the medium. To denote the energy loss after forming the complex, the energy of cadmium(II), the energy of the peptide and the energy of the complex, in vacuum and considering water molecules' dielectric effect using polarizable continuum model (PCM), were calculated. The details about the mentioned methods are depicted and explained in chapter three.

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